Eur J Vasc Endovasc Surg **19**, 625–629 (2000)
doi:10.1053/ejvs.1999.1044, available online at http://www.idealibrary.com on IDEAL®

Is Non-specific Aneurysmal Disease of the Infrarenal Aorta Also a Peripheral Microvascular Disease?*

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Objectives: *to examine whether aneurysmal disease of the aorta has a functional component in the peripheral microvasculature.*
Materials: *ten normal persons; and 15 patients who had been operated on for ruptured non-specific infrarenal aortic aneurysm months to years previously were studied.*
Methods: *blood flow rates were measured: (a) in the subcutaneous adipose tissue of the forefoot by the ^{133}xenon local washout method (perfusion through nutritive capillaries supplied by arterioles with elastin in the tunica media); and (b) in the arteriovenous anastomoses of the pulp of the first toe as measured by the heat washout method (perfusion predominantly through thick-walled tubes without elastin). Perfusion rates were measured in supine subjects at heart level, at 30 cm above and at 30 cm below heart level.*
Results: *in subcutaneous adipose tissue, the capillary blood flow rate was four times higher in patients with aneurysmal disease than in normal subjects. Both groups exhibited autoregulation of blood flow and a normal veno-arteriolar sympathetic axon reflex. Blood flow rates in the arteriovenous anastomoses of the pulp did not differ between aneurysm patients and normal subjects. Autoregulation and the axon reflex were absent in the arteriovenous anastomoses of normal subjects as well as in aneurysm patients.*
Conclusions: *non-specific aneurysmal disease of the infrarenal aorta has a peripheral functional component affecting arterioles but not arteriovenous anastomoses.*

Key Words: Aortic aneurysm; Arterioles; Arteriovenous anastomosis; Capillaries; Regional blood flow; Vascular surgery.

Introduction

The tunica media of the infrarenal aortic wall of patients with non-specific abdominal aneurysm exhibits chronic inflammation and degradation of the extracellular matrix with disorganisation and disruption of the elastic fibres.[1–4] The normal vessel architecture is destroyed[5] as the aortic wall is degraded by a synergistic combination of macrophages,[6,7] plasminogen activators,[8] the elastolytic matrix metalloproteinases[6,9,10] and other proteolytic enzymes, unbalancing the protease–antiprotease system.[7,11] Genetic, anatomical, mechanical, biochemical and acquired factors contribute to the degenerative processes, and it is no longer tenable to consider this as being simply due to atherosclerosis.[12]

The elastin disturbances cause a stiffer, less compliant, wall not only of the dilated and elongated aorta.[13] Examinations by ultrasound echo-tracking technique of the common carotid artery in patients with abdominal aortic aneurysm have also shown increased carotid stiffness in both sexes, so the disease is a generalised structural and functional disorder of the arteries.[12] Normal arterioles in the peripheral tissues such as skin, subcutaneous adipose tissue and skeletal muscle have numerous elastic fibres that contribute to local blood flow rate modulation and control. The arteriovenous anastomoses (the shunt vessels) of the pulp of the fingers and toes do not have elastic fibres, but are thick-walled tubes with well-developed smooth-muscle cells.[14]

The difference in wall structure of the two vessels, arterioles and arteriovenous anastomoses, presents an opportunity to examine whether aneurysmal disease

* Presented at the XIIIth Annual Meeting of the European Society of Vascular Surgery, 1999.
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1078–5884/00/060625+05 $35.00/0

of the aorta is a disorder that includes a functional component in the peripheral microvasculature.

Material

The examinations were performed in a prospective open study on two groups of subjects: (a) 10 normals (mean age 70 years, range 64–78; three females) and (b) 15 patients who had been previously operated on for ruptured non-specific infrarenal aortic aneurysm (mean age 69 years, range 59–82; three females). All subjects were without symptoms and clinical signs of venous or peripheral atherosclerotic disease and had normal distal segmental arterial blood pressures and four pedal pulses. None had hypertension or diabetes mellitus. The protocol was approved by the local ethical committee, and all participating subjects gave their informed, written consent.

Methods

The patients were questioned for symptoms and examined for signs of arterial and venous disease. Systemic (arm) blood pressures were recorded by sphygmomanometry, and the segmental systolic ankle blood pressures were measured by the strain gauge method. The subjects were resting on an examination couch in supine position in a room with a temperature of 21–24 °C. The blood flow rates through: (a) the subcutaneous adipose tissue in the first interstice (between first and second toe) and (b) the skin of the pulp of the first toe were measured by the methods outlined below (i) with the foot fixed and immobilised at heart level, (ii) with the foot passively positioned 30 cm below the heart level, and (iii) with the foot passively positioned 30 cm above the heart level.

The blood flow rate in the subcutaneous adipose tissue in the first interstice was measured with the local ^{133}xenon washout method after atraumatic labelling.[15,16] The measurements were made on unheated skin (temperature around 35.5 °C): 0.2–0.3 ml ^{133}Xe (555 Mbq/ml, Nordion, Europe, S.A.) dissolved in isotonic saline was introduced between the skin of the dorsal aspect of the interstice between the first and the second toes and a 20-μm-thick gas-tight, circular Mylar membrane with an inner diameter of 2.2 cm, which was attached to the skin by double adhesive tape at its circumference to create a small diffusion chamber. After 3 min the solution was withdrawn, the membrane was removed, the area wiped off, and surplus ^{133}Xe blown away. In this way, atraumatic labelling of the skin with ^{133}Xe was obtained. After a period of 35–40 min following labelling, all the ^{133}Xe was washed out from the cutaneous layer, and it was then possible to detect the washout from a completely undisturbed subcutaneous adipose tissue. The γ-rays of ^{133}Xe were recorded for 7 min at each level (heart, 30 cm down, 30 cm up) with a sampling integration time of 10 seconds by a NaI(Tl) scintillation detector (diameter 40 mm, thickness 6 mm) connected to a γ-spectrometer adjusted to the 81 keV photopeak, a rate-meter and a computer. The collimation was wide, and the distance between skin and detector was kept constant (5–7 cm). The count values were corrected for background activity and plotted against time in a semilogarithmic diagram. After curve resolution, the cutaneous blood flow rate, f_{xe}, was calculated from $f_{xe} = k_{xe} \cdot \lambda_{xe} \cdot 100$ (ml/100 g/min) where k_{xe} is the fractional washout rate constant of ^{133}Xe from subcutaneous adipose tissue, and λ_{xe} is the subcutaneous adipose tissue to blood partition coefficient for ^{133}Xe (10 ml/g).[17] The ^{133}Xe washout method applied in this manner determines blood flow rate through the capillaries of the subcutaneous adipose tissue.

The heat-washout method has recently been introduced and described in detail.[18,19] An identical procedure was used in our previous work.[14,20] A Clark-type electrode E 5250 (Radiometer a/s, Denmark) was used.[18] The electrode was constructed with a thermostatically controlled cap to ensure heat delivery in one direction only (to the skin). Contact fluid was positioned between skin and probe. The electrode was fixed on the pulp of the first toe by a double adhesive, ring-shaped membrane and silk tape, and a baseline temperature was recorded. Next, the probe was heated (usually for about 5 min) until the underlying skin reached a steady-state temperature of 41 °C as evidenced by constant heat dissipation from the probe. The heat was turned off, and the temperature, T, was recorded every 10 seconds until a stable base line temperature, T_b, was obtained after 6–10 min. $\Delta T = T - T_b$ for each recorded temperature measured every 10 s was plotted against time in a semilogarithmic diagram. The fractional rate constant, k, of ΔT versus time was used to calculate blood flow rate, f, from: $f = k \cdot \lambda \cdot 100$ (ml/100 g/min) where λ is the cutaneous tissue to blood partition coefficient of heat.[17] A λ-value of 1.0 (ml/g) was used for simplicity (exact value 0.954). The heat washout method detects the sum of the blood flow rate through arteriovenous anastomoses (shunt vessels) plus the blood flow rate through nutritive, cutaneous capillaries.[19]

Table 1. Results of the study: The blood flow rates in subcutaneous adipose tissue of the forefoot (capillaries) and in the pulp of the first toe (AV: arteriovenous anastomoses) were measured in 10 normal subjects and in 15 patients who had been operated on previously for ruptured abdominal aortic aneurysm (AAA).

	30 cm above heart level	Heart level	30 cm below heart level
	Blood flow rate (ml/100 g/min) mean (S.D.)		
Normal capillaries	2.8 [1.6]	3.7 [1.6]	2.0 [0.9]
Normal AV anastomoses	50.7 [6.8]	66.2 [10.2]	66.4 [11.2]
AAA capillaries	10.4 [6.4]	14.7 [4.1]	10.5 [4.7]
AAA AV anastomoses	48.4 [12.3]	67.5 [16.7]	67.5 [15.7]

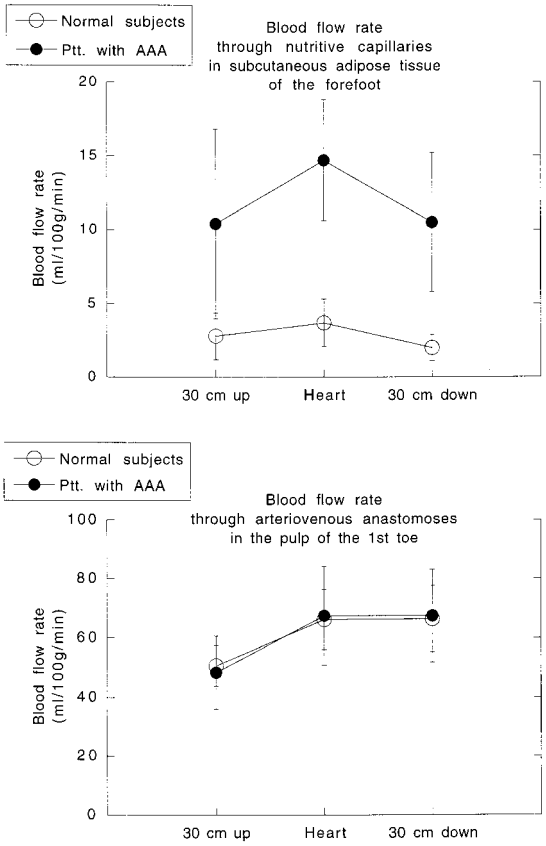

Fig. 1. (a and b) Graphic representation of the study results. Heart denotes that the results were obtained with the patient in supine position and with the foot at a level with the heart; 30 cm down and 30 cm up signify passive elevation of the foot to a level 30 cm below, respectively above, the heart level in the supine subject.

Results

The results are summarised in Table 1 and Fig. 1. The capillary blood flow rate in subcutaneous adipose tissue of the forefoot at heart level was four times higher in patients with previous rupture of an abdominal aortic aneurysm than in normal subjects ($p=0.005$ Wilcoxon signed-rank test). The blood flow rate in arteriovenous anastomoses did not differ at heart level between normal subjects and patients.

Capillary blood flow rate 30 cm below the heart was significantly reduced in both normals ($p=0.008$) and patients ($p=0.01$) as compared to the values obtained at heart level, but the blood flow rates through arteriovenous anastomoses were not. Blood flow rate 30 cm above heart level decreased neither in normal capillaries nor in the capillaries of patients with aneurysmal disease. The blood flow rate through arteriovenous anastomoses decreased significantly by elevation to 30 cm in both groups ($p=0.01$ and $p=0.001$, respectively).

Discussion

The blood flow rate in human subcutaneous adipose tissue of the distal part of the leg is, under normal circumstances, around 2–4 ml/100 g/min in young, supine subjects at a comfortable ambient temperature when the foot is level with the heart.[21] The results of the present study provided a mean value of 3.7 ml/100 g/min in this population with a mean age of 70 years, so the blood flow rate in this tissue does not seem to decrease with age in patients who have no evidence of occlusive atherosclerotic disease.

The blood flow rate in the pulp of the first toe has been previously shown to be around 50 ml/100 g/min (range 40.8–60.6) in normal subjects without vascular disease at a mean age of 43 years.[20] In the normal subjects, the blood flow rate in subcutaneous adipose tissue decreased when the leg was lowered passively to 30 cm below heart level in the supine position. This indicates that the local, sympathetic veno–arteriolar axon reflex[21,22] is functioning normally in the subcutaneous adipose tissue, in contrast to pulp skin capillaries, where the veno–arteriolar reflex is absent.[20] When the foot was elevated to 30 cm above the heart level, the blood flow rate did not differ significantly from that at heart level, so autoregulation was operative[21] in the subcutaneous adipose tissue as in the pulp skin.[14]

The heat-washout method measures both the nutritive cutaneous blood flow rate in the skin of the pulp

as well as the perfusion rate through the arteriovenous anastomoses in this area. From measurements with ^{133}xenon and heat-washouts from the toe pulp, it has been shown that about one-quarter of the value measured by the heat-washout method is due to nutritive capillary perfusion and the remainder to blood flow through the anastomoses.[20] In the present series, blood flow rate through the pulp arteriovenous anastomoses remained constant when the leg was lowered 30 cm in normal subjects, which is in accordance with previous observations in normal controls;[20] by elevation to 30 cm above heart level, blood flow rate fell to three-quarters of the rate at heart level, as in the previous series comprising middle-aged adults.[20]

It follows that arteriovenous anastomoses in normal subjects exhibit neither autoregulation, nor veno–arteriolar axon reflex in contrast to the nutritive capillaries. Below heart level, arterial and venous pressures increase in parallel as a function of the hydrostatic pressure, so the arteriovenous gradient (the driving force) is constant; above the heart, venous pressure is constant (close or equal to zero) and the arterial blood pressure decreases in proportion to the hydrostatic pressure, so the driving force diminishes accordingly by degree of elevation. The arteriovenous anastomoses consequently behave like stiff tubes in normals, but the peripheral nutritive perfusion is modulated actively with both autoregulation and veno–arterial axon reflex in operation.

In the patients with a previously ruptured aneurysm, the basic blood flow rate of subcutaneous adipose tissue was around 15 ml/100 g/min, which is four times higher than that in age- and sex-matched normal controls without vascular disease. The only conceivable explanation for this finding is that the arterioles must be more dilated during resting conditions, i.e. peripheral resistance is diminished. A theoretical objection might be that the increased blood flow rate was due to sequelae of the operation itself, for example damage to the sympathetic nerves. This is not probable, as evidenced by our previous work on normal subjects and patients reconstructed centrally as well as distally for occlusive atherosclerotic disease.[14] Besides, lesions of central sympathetic fibres result in abolishment of the veno–arteriolar axon reflex.[22]

Normal arterioles have a well-developed internal elastic membrane,[23] and the formation of periluminal corrugations of the elastic elements during vasoconstriction is not a random or passive phenomenon, but results from a highly organised smooth-muscle cell ultrastructure. There is evidence to suggest that the regular formation of ridges along the intimal border of the smooth-muscle cells allows the lumen of an arteriole to maintain an approximately circular profile during vasoconstriction.[23] The ultrastructure of arterioles in peripheral tissues of patients with aneurysmal disease is not known, but the results of our investigation clearly point towards an increase in arteriolar luminal radius under baseline conditions due to defective and disrupted elastin elements in the tunica media. The results of our study suggest that the elastic fibres determine neither the function of the veno–arteriolar axon reflex nor the blood flow rate modulation by autoregulation. Since both autoregulation and the veno–arteriolar axon reflex are present in patients with aneurysmal disease, we infer that the function of the smooth-muscle cells of the arteriolar wall is not affected by the disease, which shows that they have adapted to the change of diameter as well as the circumferential shear stress acting on the arteriolar wall.

Arteriovenous anastomoses are characterised by absence of internal as well as external elastic lamella (and bundles of microfibrils);[24] the wall is composed of an endolethium, an adventitial layer,[24,25] and a layer with two phenotypic variants of vascular smooth-muscle cells.[26] The (myo-)epitheloid cells contain a loose array of actin filaments, whereas the dense-type cells contain tightly packed parallel actin bundles.[27] Rapid closure of a canal by contraction of the smooth-muscle cells is possible. Our study showed identical qualitative and quantitative findings in arteriovenous anastomoses in normal subjects and in patients with aneurysmal disease, i.e. the arteriovenous anastomoses function normally in aneurysm patients. We have previously shown that the blood flow rate increases in arteriovenous anastomoses below heart level in patients with intermittent claudication.[14] In the present study, blood flow rate was unchanged in aneurysm patients below heart level. This can be interpreted as absence of functional atherosclerotic components in these aneurysm patients.

We conclude that non-specific aneurysmal disease of the infrarenal aorta includes a peripheral, arteriolar elastin disorder.

Acknowledgement

The Danish Heart Foundation is gratefully acknowledged for support of this study.

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Accepted 26 November 1999